

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of

Jacques DEFAYE et al.

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Application No. 10/580,856

Group 1623

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Examiner J. Lau

NOVEL CYCLODEXTRIN DIMERS AND DERIVATIVES THEREOF, METHODS FOR  
PREPARING THEM AND THEIR USE, IN PARTICULAR, FOR THE SOLUBILIZING  
PHARMACOLOGICALLY ACTIVE SUBSTANCES

DECLARATION UNDER RULE 132

Commissioner for Patents  
P.O. Box 1450  
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Sir:

I, Jacques DEFAYE, hereby declare as follows:

I am one of the inventors of the above-identified U.S.  
patent application. My relevant background and experience are  
set forth on the attached CV.

I have read the Official Action mailed March 3, 2009,  
and I am familiar with the present application. The Official  
Action rejects all claims based on an article by Ortiz-Mellet et  
al. (Chem. Eur. J. 2002, 8(9), pp. 1982-1990) in combination with  
Kotter et al. (J. Chem. Soc., Perkin Trans. 1, 1998, pp. 2193-  
2200) and Hamada et al. U.S. Patent No. 5,684,169.

I am a co-author of the Ortiz-Mellet article, and I am  
familiar with the subject matter disclosed. One of ordinary skill

in the art would have had no reason to combine the other documents with the Ortiz-Mellet article.

The Ortiz-Mellet article discloses conjugates of cyclodextrin dimer linked by a branching element to a biological marker, and that spacer arms are advantageously long. The structure may be used as a drug delivery system with taxotere as the guest compound.

The Kotter article was offered for teaching a branching element useful as a linker between saccharide moieties and in the field of carbohydrate-protein interactions, i.e., tris(2-aminoethyl)amine.

The Official Action maintained that it would have been obvious for one skilled in the art to substitute tris(2-aminoethyl)amine for the branching element of Ortiz-Mellet.

However, one of ordinary skill in the art would have been discouraged from making the proposed substitution because of the expected reduction in (1) spacer arms length, (2) ease of synthesis, and (3) biorecognition efficiency:

#### Spacer arms length

Ortiz-Mellet discloses that the spacer arm and the branching elements are two distinct elements. (See, e.g., page 1989, left column, structure 35 in figure 4.) The spacer arm connects cyclodextrin moieties to the branching element, but the spacer arm is not included in the branching elements. Thus, a

linker arm would have been required for the tris(2-aminoethyl)amine, and, at best, one would be encouraged to increase the linker arms length but not the spacer arms length.

Furthermore, the branching element tris(2-aminoethyl)amine is shorter than the two other branching elements taught in Kotter, e.g., compounds 13 and 17 on page 2195. That is, the longest chain of compound 20 is 7 atoms long (3 nitrogen and 4 carbon), whereas the longest chain of both compound 13 and compound 17 is 9 atoms long (2 oxygen and 7 carbon). Thus, at best, one would have been motivated to use compounds 13 or 17 instead of tris(2-aminoethyl)amine to comply with the teaching of Ortiz-Mellet.

#### Ease of synthesis

Ortiz-Mellet describes a branching element linked to an OAc protected carbohydrate moiety through a thiourea function.

Kotter discloses that the synthesis of a branching element linked to a carbohydrate moiety through a thiourea function is difficult when using tris(2-aminoethyl)amine. (See, e.g., Kotter, page 2194, right column, last paragraph.) When using an unprotected carbohydrate moiety the coupling yield is said to be 20%, so carbohydrate moieties protected with an OAc group were used to give a satisfying yield (page 2195, left column, last paragraph). Moreover, the deprotection reaction of the OAc group is not quantitative (82%), and the produced

compound needs purification, i.e., via chromatography. See, Kotter, page 2200, left column, paragraph c.

Thus, one skilled in the art would have been discouraged to use a branching element which would require an additional purification step.

Furthermore, Ortiz-Mellet suggests a trivalent branching element with two types of substituents: cyclodextrin and recognition element (page 1989, left column, structure 35 in figure 4.). Kotter describes trivalent branching elements having a C3 symmetry; all substituents are the same. Neither Ortiz-Mellet nor Kotter describe how to achieve such selectively functionalized branching elements.

Thus, one skilled in the art would not have been motivated to combine the teaching of Ortiz-Mellet and Kotter to synthesize a selectively functionalized branching element.

#### Biorecognition efficiency

One skilled in the art would have sought the highest binding efficiency possible.

The binding efficiency of the carbohydrate moiety is directly correlated to the biorecognition. A high binding efficiency towards a specific receptor results in a high biorecognition of this specific receptor.

Ortiz-Mellet teaches that thiourea linkers are not the best linkers for binding efficiency (page 1987, right column).

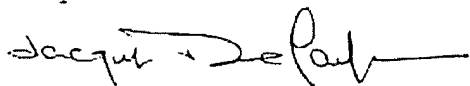
Kotter teaches that thiourea-linked clusters are not efficient (i.e., "worse inhibitor" page 2196, left column 2), but amide-linked clusters are much more efficient (See page 2196, Table 1, and page 2196 left column, paragraph 3.)

Thus, as both Ortiz-Mellet and Kotter teach that thiourea linking function is not suitable for biorecognition efficiency, one would not have been motivated to use thiourea function.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Jacques DEFAYE



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Date 06/23/09

**Curriculum Vitae**  
**Jacques DEFAYE, PhD**

**CURRENT POSITION:** **Research Director** – National Center for Scientific Research (CNRS), Emeritus  
Department of Molecular Pharmaceutical Chemistry,  
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**EDUCATION:** 1962: PhD – University of Paris, France  
1960: Research Assistant – CNRS, Institute for the Chemistry of Natural Substances (ICSN) – Gif sur Yvette  
1959: Research Intern – CNRS, Institute of Physico-chemical Biology, Paris  
1957: MS Chemistry - University of Paris, France

**PROFESSIONAL HISTORY :**

2001- present: Research Director, Emeritus

1997-2001: Associate Director of the Department of Molecular Pharmaceutical Chemistry, Institute for Molecular Chemistry of Grenoble

1982-1997: Research Director, Team Leader, Department of Condensed Matter, CEA (Center for Atomic Energy), France

1974: Visiting Professor, Ohio State University, Columbus OH, USA

1970-1982: Research Associate Professor, CNRS and University of Grenoble. Center for Plants Macromolecular Research

1963-1970: Research Associate, CNRS, Institute for the Chemistry of Natural Substances (ICSN)

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#### PATENTS:

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